Nitroxy Radical Catalyzed Oxidation of Carbohydrates

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Abstract

Nitroxy Radical Catalyzed Oxidation of Carbohydrates. JOSEPH BULLOCK (University of Kentucky, Lexington, KY 80506) Joe Bozell (National Renewable Energy Laboratory, Golden, Colorado 80401).

The oxidation of several carbohydrates to the aldaric acid was carried out to explore the possibility of making industrial products from the dicarboxylic acid. The oxidations were carried out using the catalyst 4-acetamido-2,2,6,6-tetramethyl-1-piperdinyloxy (4-acetamido-TEMPO). The carbohydrates studied were d-glucose, d-galactose, d-mannose, d-xylose, and d-arabinose. The xylose derivative, 2,3,4-trimethoxy xylose was also oxidized to determine any change in the reactivity. What we observed was a much greater selectivity and yield in the six-carbon sugars (i.e. glucose and galactose) than the five-carbon sugars (xylose and arabinose).   Mannose is a six-carbon sugar that also gave poor yields. When applied to the trimethylated derivative, the oxidation gave a mixture of products in which there appeared to be no aldaric acid.

Category: Chemistry

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Introduction

When it comes to industrial applications, organic biomass is often overlooked as a chemical feedstock. Today well over 90% of all commercially available compounds are derived from petroleum refinement. However, as fossil fuel deposits begin to wither and costs rise, we must turn to renewable sources that would be cost effective, environmentally safe, and non-toxic.

Cellulose, one of the major constituents of plant fibers, is the most abundant organic chemical on the planet.[1] It has an annual production of 100×10^9 tons and can be easily separated from the other constituents in biomass. Its abundance has made the cost of carbohydrates on the order of $0.07-$1.60 a kilogram or $0.03-$0.73 a pound. It is this availability that makes carbohydrates attractive for industrial applications. Another very attractive characteristic of carbohydrates is that they are generally non-toxic and safe to the environment. What is lacking are the chemical procedures that can turn carbohydrates into useful chemicals in good yields without using chemicals that are themselves dangerous to people and the planet.

The oxidation products of carbohydrates have been investigated for use in industry. Kiely devised a polymer synthesis[2] using the dicarboxylic acid derivative of carbohydrates. The polymerization involves the acid-catalyzed reaction of a diamine with the dicarboxylic acid. Using different carbohydrates as precursors and different diamines, an entire family of new hydroxylated nylons can be synthesized; each with its own unique physical and chemical properties. Nobes et al has already investigated some of the properties of these polymers.[3] They found that despite the numerous alcohol functional groups these polymers exhibit water-resistant properties that may be useful for

packaging. They also observed that the polymers may be able to impart water-resistivity to other materials as well.

The only roadblock that keeps the production of these polymers in the labs and out of industry is the oxidation of the carbohydrates. The polymerization reaction of to make hydroxylated nylons requires glycaric acids. Previous procedures have described an oxidation of carbohydrates using concentrated nitric acid; unfortunately this procedure gives poor yields due to over oxidation and fragmentation of the carbon chain.

The radical catalyzed oxidation of carbohydrates investigated by Merbouh[4] is an example of a high-yield chemical reaction that is done under mild conditions. This procedure uses 4-acetamido TEMPO (4-acetamido-2,2,6,6-tetramethyl-piperdinyloxy radical) as a catalyst, which is the only exotic reagent in the procedure and is used in very small amounts. It also uses commercial grade bleach (5.25% sodium hypochlorite) and sodium bromide. It is this procedure that we have investigated further in hopes of using the dicarboxylic acid products as industrial chemicals. We have done a preliminary study on the oxidation on different carbohydrates and recorded their results. We have also tried the procedure on the trimethylated derivative of xylose in hopes of obtaining a higher yield.

Materials and Methods

Figure 1 illustrates the oxidation procedure. Since the reaction generates aqueous acid yet still must be kept under basic conditions, a Titrator E526 was connected to a pH electrode and a Dosimat 655 filled with 2 M sodium hydroxide. As the pH dropped, the Titrator was programmed to release the aqueous base into the reaction mixture. A Dosimat 725 was also used to regulate the introduction of sodium hypochlorite to the

reaction mixture. Merbouh et al reported in a previous work[5] that adding the hypochlorite all at once would raise the temperature to 20-30 degrees Celsius because of the chemical reaction and cause over oxidation, so it was necessary to add the hypochlorite slowly. The temperature was monitored with a thermometer and regulated with an ice-bath. All other chemical reactions were performed with standard laboratory equipment.

All NMR analyses of the oxidized compounds were carried out on a Varian Inova 400 instrument in D_2O with deuterated propionic acid added as a reference. The products formed in the synthesis of 2,3,4-trimethoxy xylose were analyzed by NMR in $CDCl_3$.

Results

All results of the oxidations are recorded in Table 1. All compounds were synthesized as the disodium salt, then protonated with an ion-exchange resin and titrated with potassium hydroxide to (at least in the case of glucose and galactose) the less soluble and crystalline monopotassium salt. The galactarate seemed to be the less soluble as the disodium salt was observed to precipitate in small quantities. NMR data of the crude reaction mixtures indicated the presence of the oxidized material in all oxidations, however the monopotassium salts of the compounds would not precipitate to give good yields.

The synthesis of 2,3,4-trimethoxy xylarate[6] is shown in figure 2 with yields. First the anomeric position was protected with a benzyl group catalyzed by hydrochloric acid with benzyl alcohol as the solvent. There was a crude yield of 73% of the protected xylose. The methylation was done in DMSO with powedered KOH as the base with MeI; the crude yield was 93%. Deprotection was achieved by hydrogenation with 5%

palladium on carbon with hydrogen gas to yield the trimethylated xylose in a quantitative yield. The oxidation of the trimethylated derivative did not occur as readily as predicted. Since the major loss of yield from the oxidations of other sugars was over-oxidation which led to fragmentation, we hypothesized that replacing the alcohol groups with methoxy groups would lead to higher yields and greater ease of oxidation. What we observed was a mixture of products, which resembled neither the dicarboxylic acid nor the monocarboxylic acid.

Several oxidations were carried out with KOCl as the oxidation instead of NaOCl. This procedure was simpler because there was no need for an ion-exchange resin. Adding one equivalent of concentrated HCl to the reaction mixture brought the pH to approximately 3.8 and the monopotassium salt would begin to precipitate. Unfortunately there was no increase in yield.

Experimental

Oxidation of d-glucose. This procedure was identical to that cited above. Glucose (3.00 g, 16.6 mmol), 4-acetamido-TEMPO (0.04 g, 0.013 mmol), and NaBr (0.4 g, 3.36 mmol) in water (50 mL) were cooled to 0-5°C using an ice bath. The pH was adjusted to 11.5 using 2 M NaOH solution. The bleach solution (77 mL of 5.25% NaOCl, 3.3 eq/mole of glucose) was then added 1 mL/min for the first 25 mL, and then 0.25 mL/min for the rest. The Titrator E526 kept the pH between 11.4 and 11.6 with the addition of the 2 M NaOH solution. Once all the bleach solution had been added the reaction was left undisturbed for an hour to allow all the sugar to react.

After all the sugar had been consumed, the reaction mixture was concentrated to approximately 30 mL and 100 mL of 95% ethanol was added to precipitate a mixture of

disodium glucarate and some inorganic salts. After allowing the precipitate to settle, the

supernatant liquid was decanted and the remaining solid was dissolved in 30 mL water

and precipitated again with 100 mL of ethanol. This precipitation was usually kept in the

freezer overnight to allow all of the precipitate to settle to the bottom before decanting.

The remaining gummy precipitate contained some tartaric acid, gluconate, and a

few inorganic salts. To isolate the glucarate, the solid was dissolved in water (100 mL)

and approximately 35 g of freshly washed Amberlite resin was added to the solution to

protonate the carboxylic acid groups. A pH electrode monitored the pH and once it

stopped fluctuating it would settle at about 2. The Amberlite was then filtered and the

solution was titrated to a pH of 3.8 with 2 M potassium hydroxide. The solution now

contained the monopotassium salt. It was concentrated until some precipitate was

beginning to form and left in the refrigerator overnight. The precipitate was identified by

^{1}H NMR spectroscopy as pure monopotassium glucarate in 80% yield. ^{1}H NMR (D$_2$O,

400MHz): ppm 3.94 (t, 1 H, J 4.4Hz); 4.09 (dd, 1 H, J 1.2 Hz); 4.16 (d, 1 H, J 3.6 Hz);

4.19 (d, 1 H, J 2.0 Hz).

Oxidation of d-galactose. This procedure was carried out exactly as stated above

with 80% yield. ^{1}H NMR (D$_2$O, 400MHz): ppm 3.97 (s, 2 H); 4.30 (s, 2 H).

Oxidation of d-mannose. Using the same procedure as stated above, mannaric

acid was synthesized, but the monopotassium salt would only precipitate with a 2% yield.

^{1}H NMR (D$_2$O, 400MHz): ppm 3.95 (d, 2 H, J 7.6 Hz); 4.16 (d, 2 H, J 7.6 Hz).

Oxidation of d-xylose. Xylaric acid precipitated in a 5% yield only after the

removal of all tartaric acid salts. ^{1}H NMR (D$_2$O, 400MHz): ppm 4.10 (t, 1 H, J 4.4 Hz);

4.19 (d, 2 H, J 4.4 Hz).

Oxidation of d-arabinose. This procedure works poorly to give the pure monopotassium arabinarate. None precipitated after titration but NMR data indicates its presence in the reaction mixture. ^{1}H NMR (D$_2$O, 400MHz): ppm 4.05 (ddd, 2 H, *J* 4.0 Hz); 4.22 (t, 1 H, *J* 0.5 Hz).

Oxidation of 2,3,4-trimethoxy xylose. For this oxidation, the bleach solution was added at a rate of 0.25 mL/min for the first 21 mL, and then at a rate of 0.1 mL/min for the rest. Titrating yielded no precipitate as in the oxidation of arabinose.

Conclusion

The 4-acetamido-TEMPO oxidation can be applied to galactose as well as glucose with high yields and high selectivity. The oxidation of 5-carbon sugars does not proceed with as much selectivity. Protecting the secondary alcohol groups with methyl groups does not appear to increase the yield of oxidation for xylose. In order to apply this oxidation to an industrial setting, further work can be done in this field to find a more environmentally sound oxidative system that would eliminate the need for bromine. This procedure should also be tested on various other five and six carbon sugars to note any trends in the yields that we have observed.

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goes to Linda Lung and the Energy Research Undergraduate Laboratory Fellowship for providing me with a wonderful summer experience.

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6. Garcia-Martin, M., Perez, R. R., Hernandez, E. B., Galbis, J.; *Carbohyr. Res.* **2001**, *333*, 95-103

Figures and Tables
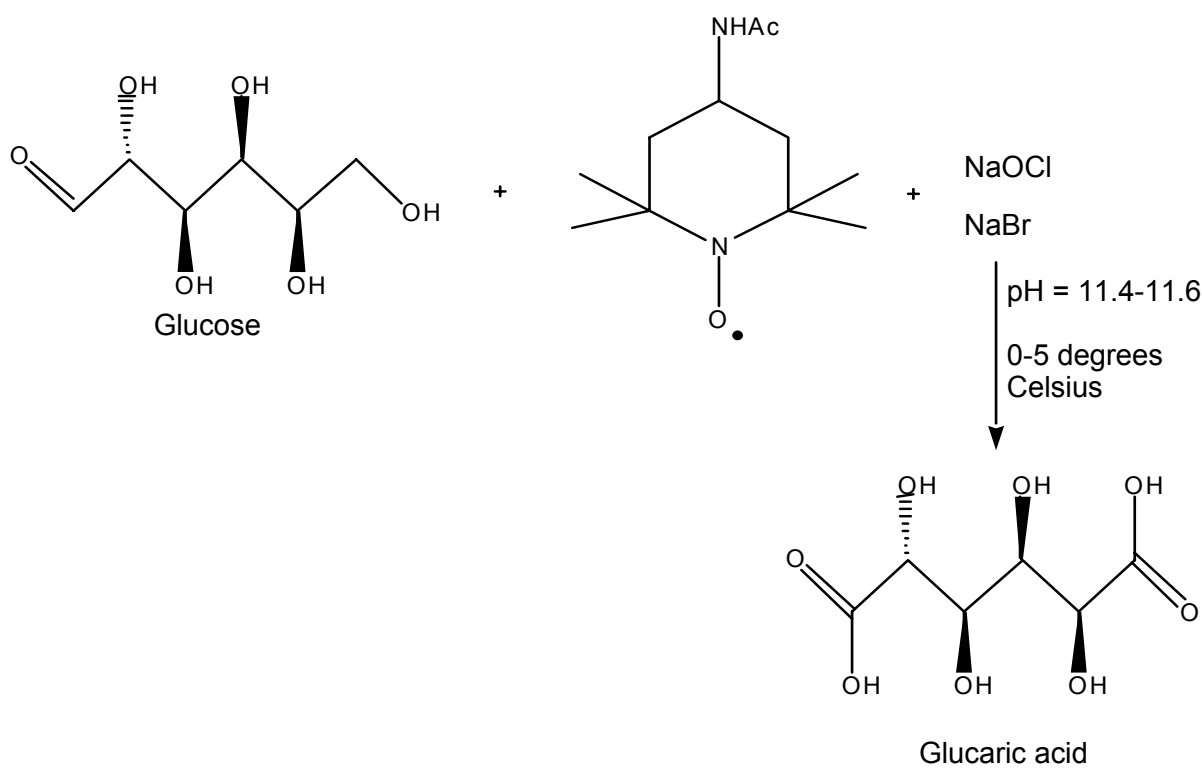
Figure 1- Oxidative schematic for glucose.
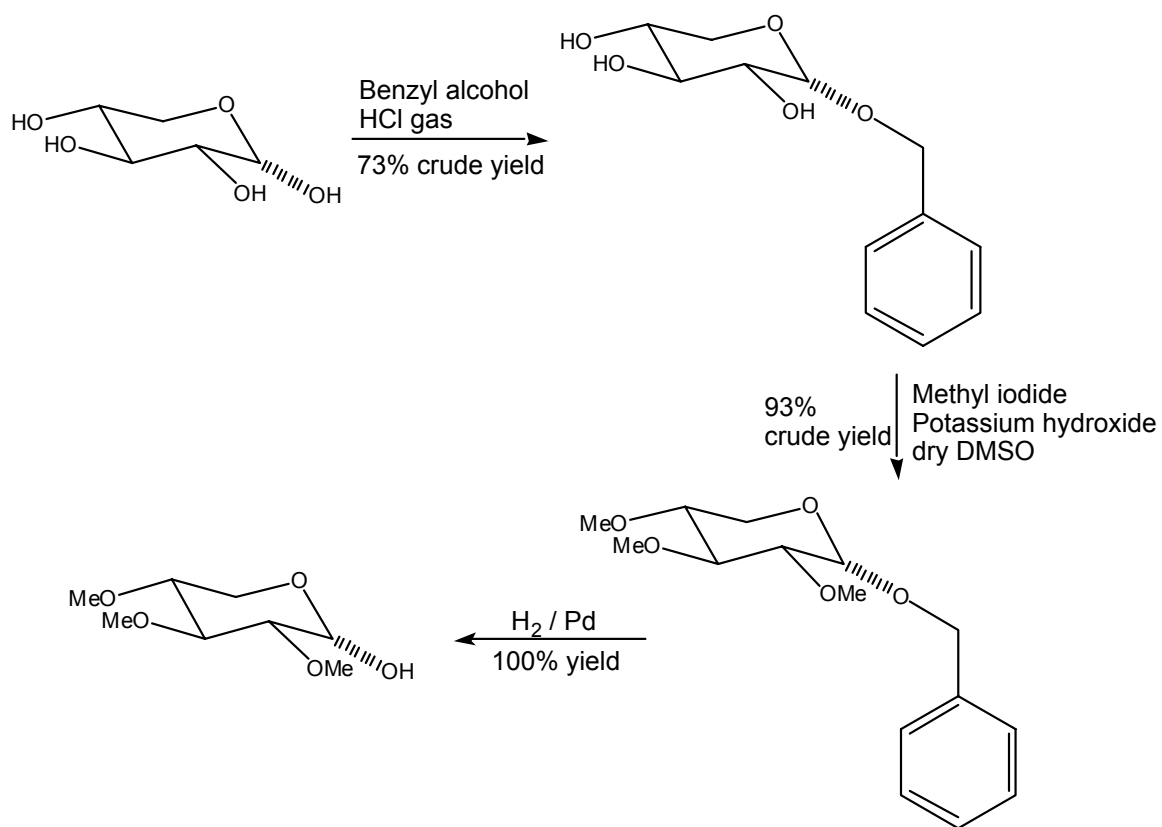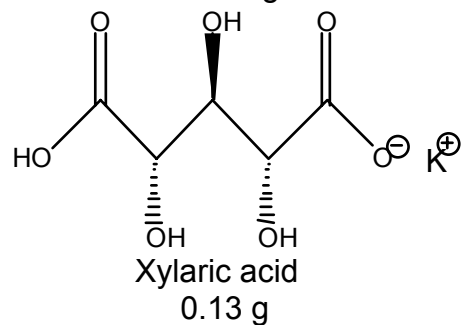
Figure 2- Synthesis for 2,3,4-trimethoxy-xylose.

D-Glucose
3.0 g

80% isolated

Glucaric acid
2.12 g isolated

D-Galactose
3.0 g

81% crude yield
80% isolated

Galactaric acid
2.11 g isolated

D-Mannose
3.0 g

2% isolated

Mannaric acid
0.07 g

D-Xylose
2.4 g
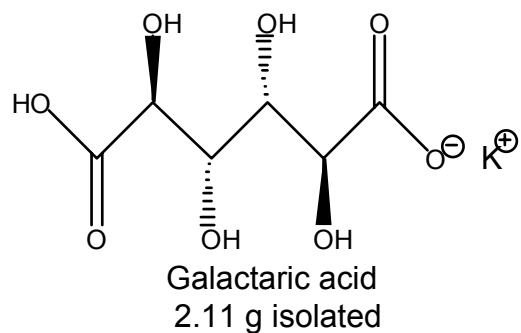
5% isolated

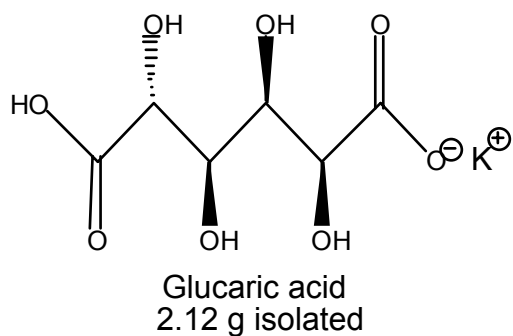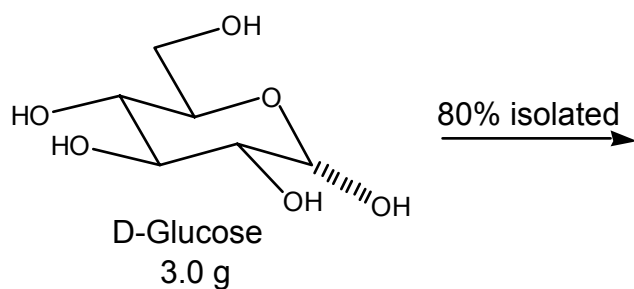Xylaric acid
0.13 g

D-Arabinose

0% isolated

Arabinaric acid
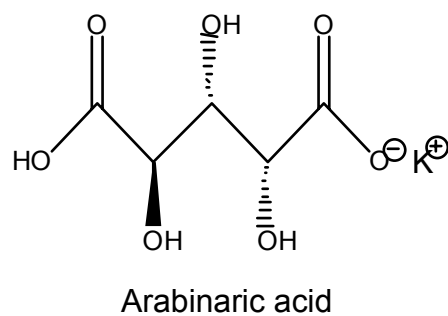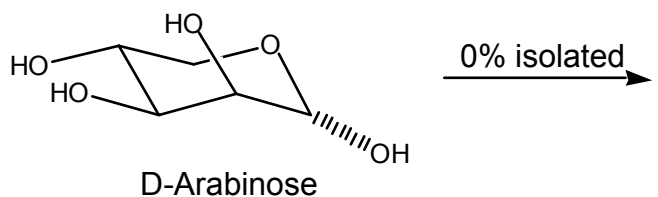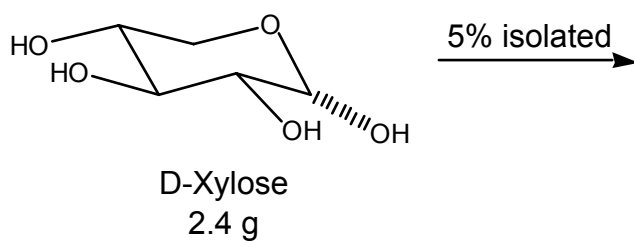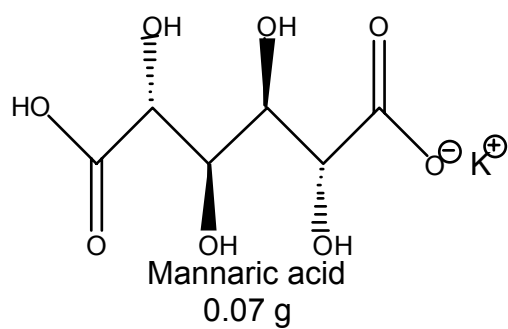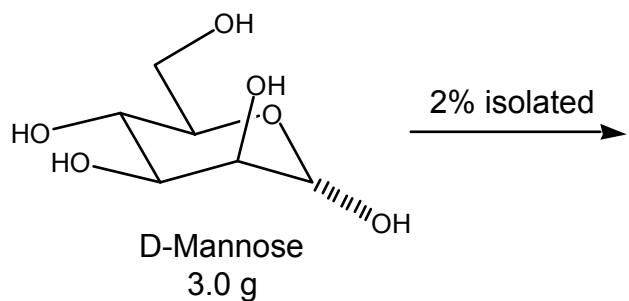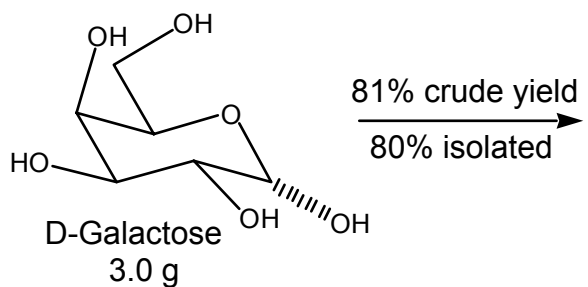
Table 1- Yields observed for oxidations. Note that the yields were from after titrating and precipitating as the monopotassium salt.